REMARKS

The Office Action

Claims 79 and 83-101 are pending in this application. Claims 79, 83, 84, 86, 88, and 91-97 are rejected under 35 U.S.C. § 112, first paragraph, for lack of written description, while claims 79, 83, 84, 86, 88, 91-97, and 101 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. Claims 79, 83-86, 90-91, and 93-99 are rejected under 35 U.S.C. § 102(b) for anticipation by McClelland et al. (WO 96/14837) as evidenced by Wetterau et al. (J. Biol. Chem. 263:6240-6248, 1988) and Breslow et al. (J. Biol. Chem. 257:14639-14641, 1982). Finally, claims 83 and 91-92 are rejected under 35 U.S.C. § 103(a) for obviousness over McClelland et al. as evidenced by Wetterau et al., Breslow et al., and French et al. (U.S. Patent No. 6,290,949), while claims 79, 83-91, and 94-100 are rejected under 35 U.S.C. § 103(a) for obviousness over Strittmatter et al. (U.S. Patent No. 5,811,243) in view of Kahn et al. (U.S. Patent No. 6,756,523) and Breslow et al. By this reply, Applicants cancel claim 79, amend claim 83, and address each of the Office's rejections.

Amendment to the Claims

Claim 83 is amended to clarify the invention of present claims 83-101. No new matter is added by the amendment.

Rejections under 35 U.S.C. § 112, first paragraph

Written Description

Claims 79, 83-84, 86, 88, and 91-97 are rejected under 35 U.S.C. § 112, first paragraph,

for lack of written description. The Office states that

> the instant specification fails to describe which amino acids to be substituted, deleted or inserted, at which positions and in which combinations, particularly at a carboxyl-terminal region of a mature, native, human apoE or at regions other than the known allelic variant sites for the various apoE isoforms and the exemplified truncated region between amino acids 186-259 of SEQ ID NO: 2, such that the encoded polypeptide having at least 90% sequence identity to an amino acid sequence comprising at least amino acids 1-185 of SEQ ID NO: 2 but without the amino acid sequence of amino acids 260-299 of SEQ ID NO: 2, still possesses the desired property, for this instance lowering the total serum cholesterol level without inducing hypertriglyeridemia. (Office Action, p. 4; emphasis in original.)

Applicants respectfully disagree but, in an effort to expedite prosecution of the present application, Applicants have cancelled claim 79 and amended claim 83 to recite that the method involves administering a replication-defective adenoviral vector having a nucleic acid molecule that encodes a secreted polypeptide consisting of amino acid residues 1-185 of SEQ ID NO:2 or amino acid residues 1-185 of SEQ ID NO:2 and one or more of amino acids 186-259 of SEQ ID NO: 2. As is acknowledged by the Office, Applicants have clearly satisfied the requirements of 35 U.S.C. § 112, first paragraph, as to present claims 83-84, 86, 88, and 91-97 (see Office Action, p. 4). Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. § 112, first paragraph, rejection of claims 79, 83-84, 86, 88, and 91-97.

Enablement

Claims 79, 83, 84, 86, 88, 91-97, and 101 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. As is discussed above, Applicants have cancelled claim 79 and amended claim 83 to recite that the method involves administering a replication-defective adenoviral vector having a nucleic acid molecule that encodes a secreted polypeptide consisting

of amino acid residues 1-185 of SEQ ID NO:2 or amino acid residues 1-185 of SEQ ID NO:2 and one or more of amino acids 186-259 of SEQ ID NO: 2. The Office acknowledges that present claims 83, 84, 86, 88, 91-97, and 101 are enabled (see Office Action, pp. 6-7). Thus, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. § 112, first paragraph, rejection of claims 79, 83, 84, 86, 88, 91-97, and 101 for lack of enablement.

Rejections under 35 U.S.C. § 102

Claims 79, 83-86, 90-91, and 93-99 are rejected under 35 U.S.C. § 102(b) for anticipation by McClelland et al. (WO 96/14837) as evidenced by Wetterau et al. (J. Biol. Chem. 263:6240-6248, 1988) and Breslow et al. (J. Biol. Chem. 257:14639-14641, 1982). The Office states:

> McClelland et al discloses at least a gene therapy method for the treatment of hypercholesterolemia, said method comprises intravenous administering...a recombinant replication defective adenoviral vector containing a DNA sequence encoding a human apolipoprotein E3 or **a fragment of human apolipoprotein E3 that is truncated at the C-terminal** (page 4, line 5 continues to line 9 of page 6; page 9, third paragraph) in a mammalian host, including a human host (page 8, last paragraph). **The C-terminal of a human apolipoprotein E3 is made up of amino acid residues 225-299 as evidenced by the teachings of Wetterau et al...** Therefore, the encoded human apolipoprotein E3 fragment that is truncated at the C-terminal that is taught by McClelland et al is an encoded human apolipoprotein E3 fragment that lacks amino acid residues 225-299...Accordingly, the method taught by McClelland et al has the same method steps and the same starting materials as the instant broadly claimed methods. Therefore, the reference anticipates the instant claims. (Office Action, pp. 16-18; emphasis in original.)

Applicants respectfully disagree.

The M.P.E.P. § 2131 states that "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." The M.P.E.P. § 2131.01 further explains that

> Normally, only one reference should be used in making a rejection under 35 U.S.C. 102. However, a 35 U.S.C. 102 rejection over multiple references has been held to be proper when the extra references are cited to:
>
> (A) Prove the primary reference contains an "enabled disclosure;"
> (B) Explain the meaning of a term used in the primary reference; or
> (C) Show that a characteristic not disclosed in the reference is inherent.

In particular, "[e]xtrinsic evidence may be used to explain but not expand the meaning of terms and phrases used in the reference relied upon as anticipatory of the claimed subject matter" (M.P.E.P. § 2131.01(II)). In addition, with respect to inherent characteristics, the M.P.E.P. § 2131.01(III) clarifies that

> "To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill."

Finally, the M.P.E.P. §§ 2112(II) and (III) state:

> There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure *at the time of invention*, but only that the subject matter ***is in fact inherent in the prior art reference***...The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic..."To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" (Emphasis in italics is original; emphasis in bold italics is added.)

In view of the guidance provided by the M.P.E.P., Applicants respectfully submit that the rejection of claims 79, 83-86, 90-91, and 93-99 under 35 U.S.C. § 102(b) for anticipation by McClelland et al. as evidenced by Wetterau et al. and Breslow et al. is improper and should be withdrawn.

McClelland et al. discloses an adenoviral vector that includes a nucleic acid encoding apolipoprotein E *or a fragment or derivative thereof*, which "may be administered to a host as part of a gene therapy treatment of hypercholesterolemia" (Abstract). McClelland et al. defines the term "fragment or derivative thereof" as follows:

> The term "fragment or derivative thereof" as used herein means that the apolipoprotein E may be a protein which has deletion(s) of amino acid residues within the protein structure, and/or may be truncated at the C-terminal and/or the N-terminal, and/or may be mutated such that one or more amino acid residues normally present in the protein structure are replaced with other amino acid residues. Such fragments and derivatives of apolipoprotein E retain the same biological activity as unmodified apolipoprotein E. (See McClelland et al., p. 4, lines 13-21; Emphasis added.)

Thus, McClelland et al. only describes generic apolipoprotein E fragments (i.e., those having unspecified deletions at the C-terminus and/or the N-terminus). McClelland et al. fails to teach or suggest the amino acid sequence of even a single apolipoprotein E deletion mutant, and certainly not the an apolipoprotein E consisting of amino acid residues 1-185 of SEQ ID NO:2 or amino acid residues 1-185 of SEQ ID NO:2 and one or more of amino acids 186-259 of SEQ ID NO: 2, as is recited in present claim 83, and claims dependent therefrom, much less an adenoviral vector encoding an apolipoprotein E having this amino acid sequence. Thus, McClelland et al. alone fails to teach or suggest each and every limitation of present independent claim 83, and claims dependent therefrom.

The Office, in view of the deficiencies in the disclosure of McClelland et al., and in an effort to establish the rejection of claims 79, 83-86, 90-91, and 93-99 for anticipation, combines McClelland et al. with Wetterau et al. and Breslow et al. The Office relies on Wetterau et al. and Breslow et al. as extrinsic evidence to demonstrate that the apolipoprotein E fragments disclosed in McClelland et al. are inherently the same as the apolipoprotein E fragments recited in rejected

claims 79, 83-86, 90-91, and 93-99. In particular, the Office relies on Breslow et al. to establish that the apoE3 nucleic acid sequence set forth in McClelland et al., which is described as corresponding to Genbank Accession No. K00396, is the same sequence as that defined in the present specification by SEQ ID NO: 15 (see Office Action, p. 17). The Office relies on Wetterau et al. to demonstrate that "[t]he C-terminal of a human apolipoprotein E3 is made up of amino acid residues 225-299" (Office Action, p. 16; emphasis omitted). Thus, the Office concludes that because "the method taught by McClelland et al has the same method steps and the same starting materials as the instant broadly claimed methods...the reference anticipates the instant claims" (Office Action, p. 18). Applicants respectfully disagree.

The Office's supplementation of McClelland et al. with Wetterau et al. is clearly improper for at least two reasons. First, the Office improperly uses Wetterau et al. to expand the meaning of the term "fragments," as it is used by McClelland et al., to encompass apolipoprotein E fragments not even disclosed or conceived by McClelland et al. As is explained by the M.P.E.P. § 2131.01, the Office must rely only on a single prior art reference in making a rejection under 35 U.S.C. 102. One exception to this rule is where the Office relies on a secondary reference to explain the meaning of a term used in the primary reference. Here, the Office relies on Wetterau et al. to provide sequence information for the phrase "apolipoprotein E fragment" used by McClelland et al. The Office states:

> The C-terminal of a human apolipoprotein E3 is made up of amino acid residues 225-299...[and t]herefore, the encoded apolipoprotein E3 fragment that is truncated at the C-terminal that is taught by McClelland et al is an encoded human apolipoprotein E3 fragment that lacks amino acid residues 225-299" (Office Action, p. 16).

The Office's decision to define the phrase "apolipoprotein E fragment" in view of Wetterau et al. can only be viewed as arbitrary. Nothing in McClelland et al. leads the skilled artisan to the specific apolipoprotein E fragment described by Wetterau et al. In fact, McClelland et al. only describes the genus of apolipoprotein E fragments containing amino acid deletions at the amino- or carboxyl-terminal ends; McClelland et al. fails to teach or suggest even a single species within that genus, and certainly not the apolipoprotein fragment described by Wetterau et al. Thus, the use of Wetterau et al. in making the present rejection expands the phrase "apolipoprotein E fragment" to include a species that was not described by or even conceived by McClelland et al. Thus, the Office's use of Wetterau et al. to explain the meaning of this phrase in fact expands the phrase, and thus, is an improper use of a secondary reference in making a rejection under 35 U.S.C. § 102.

Second, it would be improper for the Office to rely on Wetterau et al. to establish the inherent anticipation of claims 79, 83-86, 90-91, and 93-99 by McClelland et al. because the missing descriptive matter (apoE fragments lacking amino acids 225-299) is not **necessarily** present in the disclosure of McClelland et al. The C-terminal truncated apoE fragments of McClelland et al. are not defined at all. McClelland et al. certainly fails to describe the apoE fragment disclosed by Wetterau et al., and this apoE fragment, while one of many possibilities, is not **necessarily** the one described by McClelland et al. Because inherency may not be established by probabilities or possibilities (M.P.E.P. § 2112(III), *supra*), the combination of McClelland et al. with Wetterau et al. to establish the inherent anticipation of claims 79, 83-86, 90-91, and 93-99 is improper.

Furthermore, Applicants note that the Office's reliance on Breslow et al. in rejecting claims 79, 83-86, 90-91, and 93-99 under 35 U.S.C. § 102(b) does not remedy the deficiencies of McClelland et al. or Wetterau et al. because nothing in Breslow et al. establishes that the apolipoprotein E fragments described by McClelland et al. necessarily lacked amino acids 225-299. Thus, for all the reasons discussed above, the rejection of claims 79, 83-86, 90-91, and 93-99 for anticipation by McClelland et al. in view of Wetterau et al. and Breslow et al. should be withdrawn.

Rejections under 35 U.S.C. § 103

McClelland et al. in Combination with Wetterau et al., Breslow et al., and French et al.

Claims 83 and 91-92 are rejected under 35 U.S.C. § 103(a) for obviousness over McClelland et al. as evidenced by Wetterau et al., Breslow et al., and French et al. (U.S. Patent No. 6,290,949). Like the novelty rejection discussed above, the Office relies on McClelland et al for its disclosure of "a gene therapy method for the treatment of hypercholesterolemia...[by] intravenous[ly] administering...a recombinant replication defective adenoviral vector containing a DNA sequence encoding a human apolipoprotein E3 or a fragment of human apolipoprotein E3 that is truncated at the C-terminal [end]" (Office Action, p. 19; emphasis omitted). The Office further relies on Wetterau et al. as evidence that the apolipoprotein E3 fragments disclosed by McClelland et al. lack amino acids 225-299, and on Breslow et al. as evidence that the apolipoprotein E3 disclosed by McClelland et al. has the same nucleic acid sequence as that set forth by the present application in SEQ ID NO: 15. Finally, the Office relies on French et al. for its teaching of the "direct intra-arterial injection or infusion of a recombinant, replication-

defective adenoviral vector carrying gene sequences that are capable of ameliorating symptoms of cardiovascular diseases such as atherosclerosis or dyslipidemia or restenosis in a mammal" (Office Action, p. 20). In view of French et al., the Office concludes that "it would have been obvious for an ordinary skilled artisan to modify the method of McClelland et al. by also delivering the replication-defective adenoviral vector to an artery at the site of a lesion in a mammal suffering a cardiovascular disease such as atherosclerosis in light of the teachings of French et al." (Office Action, pp. 20-21). Applicants respectfully disagree that present claims 83 and 91-92 are obvious over McClelland et al., Wetterau et al., Breslow et al., and French et al., either singly or in combination.

A claimed invention is unpatentable if the differences between it and the prior art are such that the claimed subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *See* 35 U.S.C. § 103(a) (2003). Correspondingly, the conclusion regarding obviousness of a claimed invention is based upon the following four factual inquiries: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the pertinent art; and (4) secondary considerations of nonobviousness (*e.g.*, commercial success, long-felt but unsolved needs, failure of others). *See McNeil-PPC, Inc. v. L. Perrigo Co.*, 67 U.S.P.Q.2D (BNA) 1649, 337 F.3d 1362, 1368 (Fed. Cir. 2003) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)); *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1124 (Fed. Cir. 2000) (same); *Ex Parte Crinion*, No. 2001-0210, 2002 WL 31257831, at *2 (Bd. Pat. App. & Interf. 2001) (same); MPEP § 2141.

"A prima facie case of obviousness may be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. *In re Geisler*, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997)." (M.P.E.P. § 2144.05(III); emphasis added.) *See also KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1739–40 (explaining that when the prior art teaches away from a combination, that combination is more likely to be nonobvious). A reference teaches away when a skilled artisan, upon reading the reference, would be led on a divergent path from the one taken by the Applicants. Although "any need or problem known in the field of endeavor at the time of invention and addressed by the [present application] can provide a reason for combining the elements in the manner claimed" (*see KSR*, 127 S. Ct. at 1742), it is necessary for the Office to establish a sufficient basis for concluding that one skilled in the art would combine the reference teachings to yield the claimed invention. *See In re Icon Health and Fitness, Inc.*, 2007 U.S. App. LEXIS 18244, at 13-14.

As is explained in the present specification, it was known that increases in the level of wild-type apolipoprotein E beneficially promoted the clearance of cholesterol ester-rich lipoprotein remnants associated with causing premature atherosclerosis, but detrimentally increased triglyceride levels (see Specification, p. 6). Applicants discovered that the removal of amino acids 260-299 from the C-terminal end of apolipoprotein E produced a truncated apolipoprotein E capable of lowering serum cholesterol levels *without increasing the level of triglycerides*. Nothing in the prior art suggested that Applicants' truncated apoE would have this effect, and, in fact, the prior art taught away from the use of Applicants' truncated apoE.

As is discussed above, Applicants have amended present claim 83 to expedite prosecution of present claims 83-101. As amended, present independent claim 83 recites a method of treating

hypercholesterolemia by administering an adenoviral vector having a nucleic acid molecule that encodes a secreted polypeptide consisting of amino acid residues 1-185 of SEQ ID NO:2 or amino acid residues 1-185 of SEQ ID NO:2 and one or more of amino acids 186-259 of SEQ ID NO: 2. The method of present claim 83 further requires that the secreted polypeptide lower cholesterol in a mammal without inducing hypertriglyceridemia. For the reasons discussed below, one of skill in the art would not combine McClelland et al., Wetterau et al., Breslow et al., and French et al. to yield the invention of present claims 83, 91, and 92. Thus, the Office has failed to establish a *prima facie* case of obviousness against present claims 83, 91, and 92.

The Scope and Content of the Prior Art

McClelland et al.

In contrast to the invention of present claim 83, McClelland et al. only discloses the use of full-length apolipoprotein E to lower plasma cholesterol concentrations (see McClelland et al., p. 5, p. 11, and pp. 16-23); McClelland et al. fails to address the effect of expressing *a truncated apolipoprotein E* on plasma cholesterol concentrations or on triglyceride levels. Although McClelland et al. does generically describe fragments of apolipoprotein E (i.e., both N- and C-terminal deletion mutants), McClelland et al. fails to teach or suggest the amino acid sequence of even a single apolipoprotein E truncation mutant; McClelland et al. certainly fails to teach or suggest an apolipoprotein E truncation mutant lacking the C-terminal amino acids at position 260-299. In addition, McClelland et al. also fails to disclose the effect of apolipoprotein E, both full-length and truncated forms, on triglyceride levels in the treated patient. Thus, McClelland et al. is completely silent on the structure and sequence of the generically described apolipoprotein

E truncation mutants used to lower cholesterol, the function of these apolipoprotein E truncation mutants, and on the effect of these generic truncation mutants on triglyceride levels.

Wetterau et al.

To remedy the deficiencies of McClelland et al., the Office relies on Wetterau et al., which is cited by the Office for the proposition that "[t]he C-terminal of a human apolipoprotein E3 is made up of amino acid residues 225-299....[, and thus,] the encoded human apolipoprotein E3 fragment that is truncated at the C-terminal that is taught by McClelland et al is an encoded human apolipoprotein E3 fragment that lacks amino acid residues 225-299" (Office Action, p. 19; emphasis omitted). This conclusion is in error.

Wetterau et al. fails to provide any basis to conclude that the generic C-terminal apolipoprotein E3 truncation fragment described by McClelland et al. is or includes the apolipoprotein E3 proteolytic fragment consisting of amino acids 1-224 described by Wetterau et al. Wetterau et al. simply describes the proteolytic cleavage of apolipoprotein E3, which separates a protease resistant C-terminal portion of apolipoprotein E3 from a protease resistant N-terminal portion of apolipoprotein E3 (Abstract). Wetterau et al., though, fails to teach or suggest that either of these fragments is biologically active or that either fragment can or should be used to treat hypercholesterolemia according to the methods of McClelland et al. Thus, nothing in Wetterau et al. guides the skilled artisan to the use of either the C-terminal or the N-terminal fragment of apolipoprotein E3 to treat any disease or condition, much less the use of the apolipoprotein E3 lacking amino acids 225-299 for this purpose. Moreover, nothing in Wetterau et al. even suggests that an apolipoprotein E3 fragment lacking amino acids 225-299 would retain

the biological activity of full-length apolipoprotein E3, as is required by the methods of McClelland et al. Thus, for this reason alone, one of skill in the art would not combine McClelland et al. with Wetterau et al. to yield the invention of present claims 83, 91, and 92. Applicants note that Breslow et al. and French et al. do not remedy the deficiencies of McClelland et al. or Wetterau et al. because nothing in Breslow et al. or French et al. teaches or suggests the use of a secreted polypeptide consisting of amino acid residues 1-185 of SEQ ID NO:2 or amino acid residues 1-185 of SEQ ID NO:2 and one or more of amino acids 186-259 of SEQ ID NO: 2, in which the polypeptide lowers the total serum cholesterol level without inducing hypertriglyceridemia, as is recited in present claims 83, and claims dependent therefrom. Furthermore, these publications fail to overcome the deficiencies of Wetterau et al. because they fail to guide the skilled artisan to the use of an apolipoprotein E fragment that lacks amino acids 225-299. Thus, the Office has failed to establish a *prima facie* case of obviousness against present claims 83, 91, and 92.

Wetterau et al. Teaches Away from the Use of ApoE Proteins having Carboxy-Terminal Truncations

Even if Wetterau et al. could be read to direct the skilled artisan to administer an apolipoprotein E3 fragment, according to the methods of McClelland et al., to treat a disease or disease condition, which it does not, Wetterau et al. clearly directs the skilled artisan **away** from the use of apolipoprotein E fragment that *lacks the lipid-binding carboxyl-terminal end.* Wetterau et al. discloses that, following limited proteolytic cleavage of the full-length apolipoprotein E3, "[b]oth the isolated model amino- and carboxyl-terminal domains of apoE are

capable of binding to dimyristoylphosphatidylcholine," and thus "both domains have lipid-binding capabilities" (Wetterau et al., p. 6247). Yet, Wetterau et al. further clarifies that

> The precise region or regions of apoE that are the most important for its binding to a lipoprotein surface **are not known, although the carboxyl-terminal domain may be a good candidate**...We have presented evidence that it is the carboxyl-terminal region of the protein that mediates the self-association of apoE in aqueous solution...Taken together, these results suggest that the carboxyl-terminal region of apoE may be a major lipid-binding region in the protein...[A]lthough the amino-terminal domain may have lipid-binding capabilities in certain situations, on very low density lipoproteins **the carboxyl-terminal domain of apoE may play a more important role in lipid interaction**." (Wetterau et al., p. 6247; emphasis added.)

Wetterau et al. states that apolipoprotein E3 fragments that contain the C-terminal end are more likely to be those that bind to lipoprotein complexes involved in the clearing of cholesterol from the plasma, and thus, Wetterau et al. clearly directs the skilled artisan **away** from the use of a truncated apolipoprotein E3 that lacks the carboxyl-terminal end. Thus, Wetterau et al. materially teaches away from the use of Applicants' claimed apoE3 fragments that lack the carboxyl-terminal end (see *In re Geisler*, *supra*, and *KSR International Co. v. Teleflex Inc.*, *supra*). Thus, for this reason as well the skilled artisan would have no reason to combine Wetterau et al. with McClelland et al. to yield the invention of present claims 83, 91, and 92.

There is no Reasonable Likelihood of Success to Use the Truncated ApoE of Wetterau et al. in the Methods of McClelland et al.

Even if the Office disagrees that Wetterau et al. fails to teach or suggest to one skilled in the art the use of an apolipoprotein E3 fragment lacking amino acids 225-299 in the method of McClelland et al., or that Wetterau et al., in fact, teaches away from the use of this apolipoprotein E3 truncation mutant, there is still no reasonable basis in any of McClelland et al., Wetterau et

al., Breslow et al., or French et al. for the Office to conclude that one skilled in the art would be successful in using the truncated apolipoprotein E3 lacking amino acids 225-299 described by Wetterau et al. in the method of McClelland et al. The *KSR* Court recognized that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp" (*KSR*, 127 S. Ct. at 1732). Under these circumstances, "the fact that a combination was obvious to try might show that it was obvious under § 103." *Id.* That is not the case here. Rather than identify predictable apolipoprotein E3 truncation mutants that could be expressed in a mammal in order to lower plasma cholesterol levels, McClelland et al. discloses a broad genus of apolipoprotein E mutants that have "deletion(s) of amino acid residues within the protein structure, and/or may be truncated at the C-terminal and/or the N-terminal, and/or may be mutated such that one or more amino acid residues normally present in the protein structure are replaced with other amino acid residues" (McClelland et al., p. 4). Thus, any number of apolipoprotein E deletion mutants could be selected, based on McClelland et al., for use in lowering cholesterol levels. Significantly, though, Wetterau et al., which the Office combines with McClelland et al. in making the obviousness rejection, not only directs the skilled artisan away from the use of apolipoprotein E truncation mutants that lack the C-terminal residues, based on the lipid-associating properties of the C-terminal domain of apolipoprotein E3, but also fails to provide any rationale for using an apolipoprotein E3 lacking amino acids 225-299 in the treatment of any disease condition, much less to lower plasma cholesterol levels, such as in the method of McClelland et al., as is discussed above. Thus, Wetterau et al., either alone or in combination with Breslow et al. or French et al., fails to provide a reasonable expectation

that a truncated apolipoprotein E3 lacking amino acids 225-299 could be used successfully in the treatment method of McClelland et al. Thus, Applicants respectfully submit that, for all the reasons given above, the rejection of claims 83, 91, and 92 under 35 U.S.C. § 103(a) for obviousness over the combination of McClelland et al., Wetterau et al., Breslow et al., and French et al. should be withdrawn.

Strittmatter et al., Kahn et al., and Breslow et al. Fails to Teach or Suggest All of the Limitations of Present Claims 83-91 and 94-100

Claims 79, 83-91, and 94-100 are rejected under 35 U.S.C. § 103(a) for obviousness over Strittmatter et al. (U.S. Patent No. 5,811,243) in view of Kahn et al. (U.S. Patent No. 6,756,523) and Breslow et al. In applying this rejection, the Office asserts that Strittmatter et al., by suggesting the treatment of Alzheimer's disease by administering a viral vector that encodes apoE or a fragment thereof, provides motivation for one skilled in the art to practice the claimed invention using the methods taught by Kahn et al. and the apolipoprotein E3 sequence disclosed by Breslow et al. The Office states:

> It is noted that lowering cholesterol level is desirable in any mammal, particularly for an adult human, and even more for a human patient at age about 80 years old and combating Alzheimer's disease. Therefore, the treated subject by the method taught by Strittmatter et al would fall within the broad scope of a mammal in need of lowering cholesterol and also at risk of developing atherosclerosis...[I]t would have been obvious for an ordinary skilled artisan to modify the method of Strittmatter et al by also using a replication defective adenoviral vector containing a DNA sequence encoding ApoE fragments (e.g., ApoE3 fragments 1-191, 1-244, 1-266 and 1-272), including a DNA sequence encoding human ApoE3 fragments obtained from the human cDNA clone taught by Breslow et al. in light of the teachings of Kahn et al. and Breslow et al.

For the reasons outlined below, Applicants respectfully traverse this rejection.

The standard for establishing a *prima facie* case of obviousness is clearly set forth in

M.P.E.P. § 2143.03, which states (emphasis added):

> To establish a *prima facie* case obviousness of a claimed invention, *all the claim limitations* must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970).

As is discussed above, prior claim 79 has been cancelled. Thus, Applicants address this rejection as it applies to pending claims 83-91 and 94-100. As amended, claim 83, from which the other rejected claims depend, is directed to a method of lowering cholesterol in a mammal in need thereof by intravascularly administering a replication-defective adenoviral vector that includes a nucleic acid molecule that encodes a secreted polypeptide consisting of amino acid residues 1-185 of SEQ ID NO:2 or amino acid residues 1-185 of SEQ ID NO:2 and one or more of amino acids 186-259 of SEQ ID NO: 2. The polypeptide, when expressed in the mammal, lowers the total serum cholesterol level without inducing hypertriglyceridemia.

Turning to the first cited reference, Strittmatter et al. describes the treatment of Alzheimer's disease in a patient by administering apolipoprotein E, or a fragment thereof. Strittmatter et al. discloses that

> The present invention is based on the finding that ApoE3 binds avidly to the tau protein but ApoE4 does not, that neither ApoE3 nor ApoE4 binds to phosphorylated tau, and that ApoE3 binds avidly to the MAP2c protein but ApoE4 does not. Thus, the present invention provides a method of inhibiting the formation of paired helical filaments and/or neurofibrillary tangles in a cell by administering to (or introducing into) the cell either an apolipoprotein E which binds to tau (e.g., ApoE2, ApoE3), or an apolipoprotein E fragment which binds to tau in that cell. Administration may be carried out by either delivering the active agent directly to the cell, or by delivering genetic material to the cell which in turn delivers the active agent to the cell. (Stittmatter et al., col. 2, lines 26-39.)

Although Strittmatter et al. discloses administering an apolipoprotein E fragment to an Alzheimer's disease patient, such administration is not intended to treat high cholesterol levels in

the patient, nor is there any mention of this effect. Rather, the apolipoprotein E fragment is administered according to the methods of Strittmatter et al. for the sole purpose of "inhibiting the formation of paired helical filaments and/or neurofibrillary tangles" (Strittmatter et al., col. 2, lines 30-33). Nowhere does Strittmatter et al. mention or even suggest that an apolipoprotein E fragment may be used to lower high cholesterol levels without inducing hypertriglyceridemia, as is claimed.

The second cited reference, Kahn et al., does not cure the deficiencies in Strittmatter et al. Kahn et al. describes "the use of an adenovirus-derived vector for the expression of a selected nucleotide in the cells of the central nervous system" (Kahn et al., col. 2, lines 15-16). Kahn et al., like Strittmatter et al., fails to teach or suggest the use of an apolipoprotein E consisting of amino acid residues 1-185 of SEQ ID NO:2 or amino acid residues 1-185 of SEQ ID NO:2 and one or more of amino acids 186-259 of SEQ ID NO: 2 to lower cholesterol levels in a mammal in need thereof without inducing hypertriglyceridemia, as is recited in present claims 83-91 and 94-101. Accordingly, the disclosure of Kahn et al., either singly or in combination with Strittmatter et al., fails to teach or suggest each and every limitation of present claims 83-91 and 94-101.

Finally, the third cited reference, Breslow et al., does not cure the deficiencies in Strittmatter et al. and Kahn et al. As is discussed above, Breslow et al. simply discloses the isolation and characterization of "bacterial clones containing portions of human apo-E cDNA" (Breslow et al., p. 14639). In particular, Breslow et al. discloses amino acids 81-299 of apolipoprotein E3 (see Figure 3), which corresponds to amino acids 99-317 of Applicants' SEQ ID NO: 15 and amino acids 81-299 of Applicants' SEQ ID NO: 2. Breslow et al., like

Strittmatter et al. and Kahn et al., fails to teach or suggest the use of an apolipoprotein E consisting of amino acid residues 1-185 of SEQ ID NO:2 or amino acid residues 1-185 of SEQ ID NO:2 and one or more of amino acids 186-259 of SEQ ID NO: 2 to lower cholesterol levels in a mammal in need thereof without inducing hypertriglyceridemia, as is recited in present claims 83-91 and 94-101. Accordingly, the disclosure of Breslow et al., either singly or in combination with Strittmatter et al. and Kahn et al., fails to teach or suggest each and every limitation of present claims 83-91 and 94-101.

The Office's Official Notice of Facts Not on the Record to Establish the Present Obviousness Rejection is Improper

Although none of Strittmatter et al., Kahn et al., or Breslow et al., either singly or in combination, teaches or suggests the use of an apolipoprotein E consisting of amino acid residues 1-185 of SEQ ID NO:2 or amino acid residues 1-185 of SEQ ID NO:2 and one or more of amino acids 186-259 of SEQ ID NO: 2 to lower cholesterol levels *in a mammal in need* thereof without inducing hypertriglyceridemia, as is recited in present claims 83-91 and 94-101, the Office arrives at the claimed invention by taking notice that "lowering cholesterol level is desirable in any mammal, particularly for an adult human, and even more for a human patient at age about 80 years old and combating Alzheimer's disease" (Office Action, p. 22). Thus, the Office concludes, the limitation of present independent claim 83 of "lowering cholesterol level in a mammal in need thereof," is met because Alzheimer's disease patients are patients "in need of lowering cholesterol and also at risk for developing atherosclerosis" (Office Action, p. 22). This is clearly improper.

As is explained in M.P.E.P. § 2144.03(A), "[i]t would not be appropriate for the examiner to take official notice of facts without citing a prior art reference where the facts asserted to be well known are not capable of instant and unquestionable demonstration as being well-known." In the present case, the Office has taken official notice of facts used to establish the present rejection of claims 79, 83-91, and 94-101 for obviousness over Strittmatter et al., Kahn et al., and Breslow et al. without providing any evidence to support the Office's position. In particular, the Office, without evidence, has taken official notice that 1) Alzheimer's disease patients have high cholesterol levels that require lowering and are at risk for developing atherosclerosis, and 2) the skilled artisan's knowledge of this condition in Alzheimer's disease patients, coupled with the disclosures of Strittmatter et al., Kahn et al., and Breslow et al., provides the motivation and reasonable expectation of success to apply the method of Strittmatter et al. to treat high cholesterol in these Alzheimer's disease patients. Applicants respectfully challenge the Office's factual assertions as not properly officially noticed or not properly based upon common knowledge because the factual assertions are made without any evidentiary support.

Nothing in Strittmatter et al., Kahn et al., or Breslow et al. teaches or suggests *lowering cholesterol levels in a mammal in need thereof* by using an apolipoprotein E consisting of amino acid residues 1-185 of SEQ ID NO:2 or amino acid residues 1-185 of SEQ ID NO:2 and one or more of amino acids 186-259 of SEQ ID NO: 2, as is recited by present claims 83-91 and 94-101. Strittmatter et al., which is the primary reference cited by the Office in the present rejection, simply discloses the use of an apolipoprotein E fragment to inhibit the "formation of paired helical filaments and/or neurofibrillary tangles," the appearance of which, along with the deposition of amyloid beta-peptide (AP), is "generally accepted to be better correlated" with the

development of dementia in Alzheimer's disease patients (see Strittmatter et al., col. 1, lines 55-62, and col. 2, lines 30-33). Thus, nothing in Strittmatter et al. teaches, suggests, or motivates the skilled artisan to practice the method of present claims 83-91 and 94-101. Because the Office has failed to provide any evidence that supports the rationale upon which the Office rejects claims 79, 83-91, and 94-101, Applicants respectfully request that the rejection of claims 79, 83-91, and 94-101 under 35 U.S.C. § 103(a) for obviousness over Strittmatter et al. in combination with Kahn et al. and Breslow et al. be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested.

Enclosed is a petition to extend the period for replying for one month, to and including October 1, 2007, as September 30, 2007, fell on a Sunday, and a check for the fee required under 37 C.F.R. § 1.17(a). If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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